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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,355	12/03/2003	Ih-Jen Su	70001-020001	5446

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

INFO@ORTPATENT.COM

Office Action Summary	Application No.	Applicant(s)	
	10/727,355	SU ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30,32-35,37-40 and 42* is/are pending in the application.

4a) Of the above claim(s) *1-26,30,35,40 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-29,32-34 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on May 14, 2008.

Currently, claims 27-29, 32-34, and 37-39 are under examination on the merits.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

Claims 27-29 and 32-34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Morrissey et al., Paul et al., Stuyver et al., and Linnen et al. for the reasons of record as set forth in the Office action mailed on February 21, 2008 and for the reasons stated below.

Applicant's arguments filed on May 14, 2008 have been fully considered but they are not persuasive. Applicant argues that since RNAi was known to be highly unpredictable, one of ordinary skill in the art would not have predicted that an RNAi molecule targeted to SEQ ID

NO:3 would inhibit HBsAG level completely, thereby arguing for an unexpected result. In so doing, applicant provides two non-patent literature references: Cheng et al. (Exhibit A) and McCaffrey et al. (Exhibit B). Contrary to applicant's argument that the instantly claimed RNAi molecule comprising SEQ ID NO:3 is a potent inhibitor to the extent that it is "unexpected", the two non-patent literature references, Exhibit A and Exhibit B, further corroborate the *prima facie* obviousness of selecting SEQ ID NO:3 as the target sequence for inhibiting HBV via RNAi mechanism for the following reasons:

First, as previously stated in the Office action dated February 21, 2008, the instantly claimed target sequence of SEQ ID NO:3 comprising "GGTATGTTGCCCGTTTGTC" is extremely well-conserved throughout a number of different subtypes of HBV genomic sequences as evidenced by the "boxed" nucleotide sequences depicted in Figure 1D of Stuyver et al. Note that the "boxed" nucleotide sequences are faithfully, that is 100%, conserved among the 32 different subtypes of HBV genomic sequences. Furthermore, the highly conserved HBV genomic sequence comprising SEQ ID NO:3 was therefore used as HBV amplification and sequencing primer sequence as evidenced by the SEQ ID NO:75 of Stuyver et al. and SEQ ID NO:15 of Linnen et al. Even better, the instantly claimed target region (HBsAg) comprising SEQ ID NO:3 was also known to be the target region for antibody-based protection against HBV infection of "all subtypes" as taught by Stuyver et al. Although one skilled in the art might not have predicted 100% or complete abolition of HBV expression by targeting the "boxed" region of HBsAg in Figure 1D of Stuyver et al., the skilled artisan would have reasonably predicted a far better or potent inhibition of HBV expression by an RNAi molecule targeted to the nucleotide sequence of the well-conserved HBsAg region as represented by the "boxed" region of Figure

1D of Stuyver et al., compared to RNAi molecules targeted to other regions of the HBV genomic sequence.

Second, such reasonable, scientific fact-based prediction (that is, targeting a highly conserved, antibody-target region, primer target region would yield a higher degree of HBV inhibition than targeting a less well-conserved region of HBV genomic sequence) is indeed reflected in actuality as shown in the teachings of "Exhibit A", wherein "HBsAg-3" siRNA or shRNA molecule that is targeted to SEQ ID NO:3 of the instant application is more potent than "HBsAg-1" molecule that is targeted to a less well-conserved HBsAg region of the HBV genomic sequence. See Figure 2. Since making a number of siRNA molecules targeted to different regions of a target gene and experimentally testing their ability to inhibit target gene expression was a routine experimental process in the art as part of screening for and identifying the most optimal and potent siRNA molecule, as evidenced by the teachings of "Exhibit A" (a total of 12 different RNAi molecules were synthesized and tested including negative controls) or "Exhibit A" (a total of 8 different RNAi molecules were synthesized and tested including a negative control) or the teachings of Morrissey et al. (a number of different nucleic acid inhibitors were synthesized and tested).

Third, contrary to applicant's argument that the inhibitory potency of SEQ ID NO:3 is "unexpected", the disclosure of "Exhibit A" shows otherwise: four siRNA candidate molecules (HBsAg-3, HBsAg-7, HBsAg-9, and HBsAg-10) out of ten show complete abolition of HBsAg expression when transfected into cultured cells. See Figure 2. Hence, it is unclear who applicant can argue that the inhibition level of the instantly claimed RNAi molecule is unexpected when there are other RNAi molecules as effective as the claimed RNAi molecule. Furthermore, it is

even more clear that the inhibitory potency of the instantly claimed RNAi molecule is not to the extent that it is truly unexpected in view of the disclosure of "Exhibit B", wherein even other RNAi molecules comprising different, non-overlapping HBV target sequences from the instantly claimed target sequence of SEQ ID NO:3 are able to inhibit HBsAg expression in cultured cells to the level that only less than 10% HBsAg is expressed after RNAi treatment. See "HBVU6no.2" and "HBVU6no.6" depicted in Figure 2. Even further, one of the first prior art publications pertaining to 21-nucleotide siRNA (19-base pairs with 2-nucleotide overhang)-mediated RNAi in cells also showed that siRNAs are capable of inhibiting target gene expression almost completely. See Figure 2 of Elbashir et al. (*Nature,* 2001, 411:494-498), which is cited by both Morrissey et al. (US 2003/0148985 A1, citation of record) and Paul et al. (*Nature Biotechnology,* 2002, 29:505-508, citation of record). Taken together, the alleged "unexpected result" pertaining to the instantly claimed RNAi molecule comprising SEQ ID NO:3 is not found to be persuasive because other anti-HBV RNAi molecules than the one that is claimed in the instant case can inhibit HBsAg expression as much and as effectively as the instantly claimed RNAi molecule comprising SEQ ID NO:3, as evidenced by the showings of Exhibit A and Exhibit B, and because the strong inhibitory potency of siRNA molecules (e.g., almost complete inhibition of target gene expression in cells) was known in the art as taught by Elbashir et al. In other words, the strong inhibition of target gene expression of the instantly claimed RNAi molecule is not an unexpected, unique property that is demonstrated only by the claimed RNAi molecule, but rather is observed by other related or unrelated RNAi molecules. As such, the fact that other anti-HBV siRNAs are as effective as the claimed siRNA is not an unexpected result sufficient to establish unobviousness within the meaning of 35 U.S.C. 103.

Finally, even if one of ordinary skill in the art were unaware of the scientific fact and knowledge that the instantly claimed SEQ ID NO:3 is located within a favorable HBV target region as taught by Morrissey et al., Stuyver et al., and Linnen et al., the skilled artisan would have successfully obtained the instantly claimed RNAi molecule comprising SEQ ID NO:3 and would have used it to inhibit HBV replication in a cell, because art-recognized standard siRNA design/selection guidelines were available to all skilled artisans working in the RNAi technology at the time of the invention. For instance, it was widely known in the art to make and test several siRNA molecules, which are designed by following the specific guidelines set forth by Elbashir et al. (either *Nature,* 2001, 411:494-498 or *Methods,* 2002, 26:199-213) at the time of the invention. More specifically, Elbashir et al. taught to select a 19-mer siRNA target sequence preceded by the "AA" dinucleotide sequence, followed by synthesizing several siRNA duplexes, including negative controls, and verifying the inhibitory activities of the synthesized siRNA duplexes. See pages 202-213 of *Methods*, or the siRNA duplex sequence for "GL2" in Figure 1 and page 497 of *Nature,* wherein all of the target sense sequences of exemplified siRNAs are preceded by "AA". Concordant with the teachings of Elbashir et al., the instantly claimed 19-mer target sequence of SEQ ID NO:3 is preceded by an "AA" dinucleotide sequence. See the nucleotide sequences in the "boxed" region in Figure 1D of Stuyver et al. Hence, one of ordinary skill in the RNAi art following the art-recognized siRNA design/selection guidelines such as the conventional method of Elbashir et al. would have reasonably synthesized the instantly claimed siRNA molecule comprising SEQ ID NO:3 as one of many candidate anti-HBV siRNA molecules and would have selected the instantly claimed siRNA molecule comprising SEQ ID

NO:3 as one of the most desirable anti-HBV siRNA molecules after testing the inhibitory activities of the candidate siRNA molecules.

In light of the above, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing, and therefore this rejection is maintained.

Claims 37-39 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Morrissey et al., Stuyver et al., Linnen et al., and McCaffrey et al. for the reasons of record as set forth in the Office action mailed on February 21, 2008 and for the reasons stated below.

Applicant's arguments filed on May 14, 2008 have been fully considered but they are not persuasive. Applicant restates the same reasons for claims 27-29 and 32-34. Hence, for the same reasons as stated above (pages 2-6) of this Office action, this rejection is maintained.

Conclusion

No claim is allowed.

This application contains claims 1-26, 30, 35, 40, and 42 drawn to an invention nonelected without traverse in the reply filed on October 19, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, from 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635